The many faces of testosterone

Jerald Bain

Department of Medicine, Department of Obstetrics and Gynecology, University of Toronto, Ontario, Canada; Division of Endocrinology and Metabolism, Mount Sinai Hospital, Toronto, Ontario, Canada

Abstract: Testosterone is more than a "male sex hormone". It is an important contributor to the robust metabolic functioning of multiple bodily systems. The abuse of anabolic steroids by athletes over the years has been one of the major detractors from the investigation and treatment of clinical states that could be caused by or related to male hypogonadism. The unwarranted fear that testosterone therapy would induce prostate cancer has also deterred physicians form pursuing more aggressively the possibility of hypogonadism in symptomatic male patients. In addition to these two mythologies, many physicians believe that testosterone is bad for the male heart. The classical anabolic agents, 17-alkylated steroids, are, indeed, potentially harmful to the liver, to insulin action to lipid metabolism. These substances, however, are not testosterone, which has none of these adverse effects. The current evidence, in fact, strongly suggests that testosterone may be cardioprotective. There is virtually no evidence to implicate testosterone as a cause of prostate cancer. It may exacerbate an existing prostate cancer, although the evidence is flimsy, but it does not likely cause the cancer in the first place. Testosterone has stimulatory effects on bones, muscles, erythropoietin, libido, mood and cognition centres in the brain, penile erection. It is reduced in metabolic syndrome and diabetes and therapy with testosterone in these conditions may provide amelioration by lowering LDL cholesterol, blood sugar, glycated hemoglobin and insulin resistance. The best measure is bio-available testosterone which is the fraction of testosterone not bound to sex hormone binding globulin. Several forms of testosterone administration are available making compliance much less of an issue with testosterone replacement therapy.

Keywords: testosterone, androgens, male hypogonadism, anabolic steroids

As we age, the body undergoes multiple degenerative changes at multiple sites and in multiple systems. The changes of aging are inevitable and inexorable and represent the march toward ultimate death. We are mortal beings whose destiny it is to die. As we come to learn about the processes of life we can better prepare ourselves for the finality of death and on the way perhaps retard the degenerative process, or repair it (for however long we may enjoy this repair), or substitute chemical compounds that our bodies once produced in abundance, an abundance which fades with the advance of age.

Among the changes which occur with aging are those that affect several aspects of the endocrine system which reduces its secretions to varying degrees in different individuals. These reductions in secretions are identified by a poor but widely recognized appellation, the "pauses": menopause (decreased ovarian function), adrenopause (decreased adrenal function, especially with regard to dehydroepiandrosterone secretion), somatopause (decreased growth hormone production), andropause (decreased hypothalamic-pituitary testicular function with diminished testosterone availability and impaired spermatogenesis) (Lamberts 1997).

No one will argue with the well-established fact that the dramatic lows of testosterone as seen in castration or other significant primary testicular disturbances such as those induced by chemotherapy, radiation therapy, congenital problems, or as seen

Correspondence: Jerald Bain
Mount Sinai Hospital, Ste 1501,
600 University Ave, Toronto,
Ontario M5G 1X5, Canada
Tel +1 416 586 4436
Fax +1 416 586 3134
Email j.bain@utoronto.ca

in secondary testicular insufficiency (eg, large compressive pituitary or hypothalamic tumors) produce dramatic signs and symptoms of testosterone deficiency that require testosterone replacement therapy. Less clear, or at least more controversial, is the necessity of treating the gentler reduction of testosterone seen in the aging process.

That testosterone decreases with age has been clearly established by many studies over many years in several different populations of men (Harman et al 2001; Feldman et al 2002; Araujo et al 2004; Kaufman and Vermeulen 2005). Of even greater significance is the steeper fall of the most biologically active fraction of total testosterone, non-sex hormone binding globulin (SHBG)- bound testosterone, or bioavailable testosterone (bio-T). The classical, but not the only approach to measuring bio-T, is to precipitate out SHBG (and hence the testosterone which is strongly bound to it as well) and measure the remainder as total testosterone (Tremblay 2003). Vermeulen et al (1999) have devised a less tedious and less expensive method of measuring a surrogate for bio-T, namely calculated bio-T, inserting total T, albumin, SHBG and a constant into a mathematical formulation. There is a strong correlation between actual bio-T and calculated bio-T (Emadi-Konjin et al 2003).

Does the diminution that age brings with it in both total and bioavailable T have any clinical significance? This question leads us to the theme of this paper, "The Many Faces of Testosterone". If testosterone were simply a "sex hormone" involved only with sexual desire and arousal we might tend to dismiss testosterone treatment in the aging man as merely a "life-style" therapy without any substantive basis for broad physiological necessity. The fact is, however, that the sexual attributes of testosterone are the least of its physiological necessities and that testosterone has a broad spectrum of demonstrated physiological functions as well as a wide variety of physiological and pathophysiological associations about which we are just learning.

The many faces of testosterone

Testosterone is everywhere playing multiple roles from intrauterine life to advanced age. Table 1, the contents of which are always undergoing change primarily because of newly observed associations, provides an overview of the bodily systemic functions and patho-physiological states in which testosterone finds itself implicated. In some of these states there is a clear physiological cause and effect relationship. In others, evidence of the physiological role is early or tenuous.

Table 1 The many faces of testosterone

1. Intrauterine life in a 46XY fetus
2. Puberty
3. Classical hypogonadism
4. Post-menopausal women
5. Bones
6. Muscles/frailty
7. Libido
8. Erectile function
9. Cognition
10. Mood
11. Erythropoiesis and anemia
12. Coronary artery disease
13. Obesity
14. Diabetes mellitus
15. HIV AIDS
16. Autoimmune Disease
17. Narcotic dependence
18. Age-related hypogonadism

Intrauterine life in a 46 XY fetus

A 46 XY fetus is destined to become a male because the Y chromosome carries testicular determining gene which initiates transformation of the undifferentiated gonad into testes (Töhönen 2003). The testes subsequently produce both Mullerian Inhibiting Factor (to induce degeneration of the Mullerian system, the internal female ductal apparatus) and testosterone (to stimulate growth and development of the Wolffian system – epididymus, vas deferens, seminal vesicle and, after conversion to dihydrotestosterone (DHT) by the enzyme 5-α-reducase, the prostate gland). DHT is also the primary androgen to cause androgenization of the external genitalia.

If in a 46 XY individual testosterone is either not produced in adequate concentrations as in gonadal dysgenesis (MacLaughlin and Donahue 2004), or in the absence of the enzyme 17 alpha-hydroxylase so that testosterone is not produced (Ergun-Longmire et al 2006), or testosterone androgen receptors are absent as in the androgen insensitivity syndrome (Hughes and Deeb 2006), phenotypic females will result.

Puberty

Puberty occurs when there is an "awakening" of the hypothalamic-pituitary axis. The hypothalamus increases its secretion of gonadotropin releasing hormone (GnRH) which in turn stimulates the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH). This leads to a significant increase in the production of testicular testosterone and the induction of the well-known secondary

Table 2 Symptoms or findings of low testosterone

Weakness
Fatigue
Lethargy
Mood changes – dysthymia
– depression
– irritability
Decreased libido
Decreased erectile function
Decreased quality of orgasm
Decreased muscle mass
Decreased motivation
Loss of self-confidence
Decreased energy
Anemia
Osteopenia/osteoporosis
Decreased facial, axillary, pubic hair
Insomnia
Flushes

sex characteristics associated with puberty: growth spurt, increased libido, increased erectile function, acne, increased body hair, increased muscle mass, deepening of the voice, spermatogenesis, gynecomastia (usually transient).

Classical hypogonadism

Testosterone treatment is unequivocally needed in classical hypogonadism for reasons discussed in subsequent subsections. In classical hypogonadism, testosterone production is usually clearly below the lower limit of normal and patients are highly symptomatic; the various symptoms are easily related to the deficiencies in various bodily systems where testosterone action is important. Symptoms of testosterone deficiency are listed in Table 2. A few prominent causes of classical hypogonadism are listed in Table 3.

Post-menopausal women

With the decline of ovarian function in menopause, not only do estrogen levels decline, but so does testosterone availability, since the ovaries contribute, either by direct secretion or through precursor production, about 50 percent of circulating testosterone. The other 50 percent is supplied by the adrenal glands. Many post-menopausal or oophorectomized women are symptomatic as a consequence of reduced testosterone, the leading symptom being loss of libido (Sherwin and Gelfand 1987; Simon et al 2005). There is an increasing trend toward testosterone supplementation in these women. Such supplementation may also lead, not only to increased libido, but to increased bone mineral density and an improvement in general overall sense of well-being including energy, strength, motivation and mood (Davis et al 1995; Davis et al 2000).

Bones

Testosterone has two major effects on bones: (a) through conversion to estradiol by way of the enzyme, aromatase, testosterone inhibits osteoclastic activity and hence bone resorption; and (b) through conversion to DHT via 5-α-reductase, it stimulates osteoblastic activity and so enhances the laying down of bone (Tivesten et al 2004; Davey and Morris 2005). Hypogonadal men are at risk for the development of osteopenia or osteoporosis and hence for subsequent fracture (Fink et al 2006). About one-third of all osteoporotic hip fractures occur in men and the risk of any osteoporotic fracture in men over 50 is as high as 25 percent (Seeman 1997; Adler 2006). Although treatment with testosterone in hypogonadal men increases bone mineral density (Katznelson et al 1996), it has not yet been established that this results in a reduction in fracture rate.

Muscles/frailty

Testosterone retains nitrogen and is an essential ingredient in the development and maintenance of muscle mass (Sinha-Hikim et al 2006). With a diminution in testosterone, muscle mass diminishes as does strength. Weakness and fatigue result. A number of studies have demonstrated the ability of testosterone to restore lean body mass (muscle) in hypogonadal men, while at the same time causing a reduction in fat mass (Wang et al 2004). Treatment of hypogonadal men with testosterone results in improvement in overall physical performance as well as strength as assessed by, eg, hand grip power (Page 2005). Because of decreased muscle strength and impaired balance, older hypogonadal men are susceptible to falling and since they may already be osteopenic or

Table 3 Selected causes of classical hypogonadism

A.	Primary Hypogonadism (Testicular Causes – High LH and FSH)
	Castration
	Testicular trauma
	Klinefelter's Syndrome
	Orchitis
	Chemotherapy
	Radiation therapy to the testes
B.	Secondary Hypogonadism (Hypothalamic-Pituitary Causes-Low LH and FSH)
	GnRH insufficiency (idiopathic or Kallmann's syndrome)
	Pituitary or hypothalamic tumour
	Hyperprolactinemia
	Pituitary surgery

osteoporotic as a consequence of hypogonadism, they are at increased risk for fracture as a result of the fall (Szulc et al 2003). Men with low levels of testosterone as in androgen deprivation therapy for prostate cancer, have a significant decrease in lean body mass and hemoglobin, while at the same time they experience an increase in weight, body fat and body mass index (Smith et al 2002). Treatment of frail hypogonadal men with testosterone, therefore, can result in changes in muscle gene expression, increased muscle mass, improvements in strength, power and endurance and improved physical function.

Libido

Testosterone has several positive effects on sexual function, but its most significant effect is on libido, sexual interest and arousal. Boys going through puberty develop an enhanced interest in sex (thoughts, fantasies, masturbation, intercourse) as a consequence of rising levels of testosterone. Hypogonadal men usually have a significant improvement in libido when TRT is initiated (Wang et al 2000; Morley and Perry 2003).

Erectile function

Testosterone does play a minor role in generation of erections (Mills et al 1992) but its impact upon erections can often be seen in hypogonadal men who do not respond to sildenafil citrate until testosterone is added to the therapeutic regimen (Kalinchenko et al 2003; Rosenthal et al 2006).

Testosterone makes a contribution to nitric oxide formation. Nitric oxide, released from penile nerves stimulates guanylate cyclase which catalyzes the transformation of guanosine-5-triphosphate into 3',5'-cyclic, guanosine monophosphate (cyclic GMP). Gyclic GMP causes vasodilatation and hence erection formation (Morelli et al 2005). The breakdown of cyclic GMP to GMP is mediated by the enzyme, phosphodiesterase type-5, the inhibitors of which (eg, sildenafil citrate) enhance erection formation and maintanence (Carson and Lue 2005).

Cognition

Testosterone functions within the brain. There are several lines of evidence for this: there are androgen receptors within the brain; testosterone is converted to both dihydrotestosterone (DHT) and estradiol by the actions of 5-α-reductase and aromatase respectively in the brain; steroid hormones promote neuronal cell growth and survival (Azad et al 2003). Testosterone enhances cerebral perfusion in hypogonadal men and that perfusion takes place specifically in Brodman areas 8 and 24, regions of the brain that are concerned with: strategic planning, higher motor action, cognitive behaviors, emotional behavior, generalized emotional reaction, wakefulness and memory (Greenlee 2000; Azad et al 2003). Studies of cognition demonstrate that older men with higher levels of free testosterone index (a surrogate measure of bioavailable testosterone) have better scores in tests of: visual memory, verbal memory, visuospatial functions and visuomotor scanning. Hypogonadal men have lower scores in tests of memory, visuospatial function, with a faster decline in visual memory (Moffat et al 2002). In a very small, short term placebo-controlled study hypogonadal men with Alzheimer's Disease (AD) treated with testosterone demonstrated a modest improvement in a cognition assessment score in AD (Tan and Pu 2003).

Both men and women with Alzheimer's Disease were found to have an increased concentration of SHBG and decreased free androgen index when compared with controls (Paoletti et al 2004). In a prospective study of 574 men whose baseline age span was 32–87 years and who were followed for a mean of 19.1 years (range, 4–37), the risk of developing Alzheimers' Disease decreased 26 percent for each 10 unit increase in free testosterone index. The authors concluded that testosterone may be important for the prevention and treatment of AD (Moffat et al 2004).

Mood

Many studies demonstrate an improvement in mood of hypogonadal men treated with testosterone (Wang et al 1996; Azad et al 2003). The relationship between testosterone status and mood, particularly depression, remains unresolved. Using Beck's Depression Inventory, Barrett-Connor and colleagues found that the depression score worsened as men aged, exactly at a time when testosterone levels are decreasing (Barrett-Connor et al 1999). Pope and colleagues found that testosterone treatment in men with refractory depression lowered the Hamilton Depression rating scale and the Clinical Global Impression severity rating (Pope et al 2003). The Beck Depression Inventory remained unchanged in Pope's study.

That there is an association between depression and testosterone concentration seems possible because of the observation that depression may be associated with reduced testosterone concentrations, hypogonadal men may have their symptoms of depression relieved by TRT and that testosterone itself may have anti-depressant properties (Pope et al 2003). The evidence, however, is inconsistent. Seidman and colleagues (2002), for example, found that there was

no relationship between testosterone and depression but there was an association of testosterone with dysthymia. McIntyre and colleagues (2006), on the other hand, found that middle-aged men with depression did have a reduction in bio-available testosterone.

Erythropoiesis and anemia

Testosterone is a stimulant of hematopoiesis in the bone marrow and consequently, increases the hematocrit (Shahidi 1973). Men with unexplained anemia should have their testosterone measured and if reduced, these men should be treated with testosterone. Because of the erythropoietin stimulating effect of testosterone, one of the parameters to be monitored during testosterone treatment is hematocrit since a small percent of testosterone-treated men develop polycythemia.

Bhatia et al (2006) studied 70 male patients with type2 diabetes mellitus (age range 24–78 years). Thirty-seven subjects were found to have hypogonadism based on a calculated free testosterone level of less than 6.5 μg/dl. The hypogonadal group had a statistically significant lower hematocrit. Anemia was observed in 23% of the patients (16 out of 70). In 14 of 15 anemic patients calculated free testosterone was low.

Coronary artery disease

Before the ready availability of non-injectible testosterone preparations, and because of their ease of administration by the oral route, 17-alkylated steroids were popular surrogate agents for testosterone. These substances, however, were capable of inducing several risk factors for coronary artery disease (Kopera 1993; Hall and Hall 2005) and as a consequence, particularly after the revelations of extensive 17-alkylated anabolic steroid abuse by athletes, testosterone, became unjustly incriminated. The evidence, however, tends to suggest just the opposite; testosterone may even be cardioprotective. Dunajska and colleagues have demonstrated that when compared to controls, men with coronary artery disease tend to have: lower total testosterone levels and free androgen indices, more abdominal fat, higher blood sugar and insulin levels (Dunajska et al 2004).

Intracoronary artery infusion of testosterone causes significant coronary artery dilatation and not constriction as previously thought (Webb et al 1999). When degree of coronary obstruction is assessed by angiography, there is a direct relationship between degree of coronary artery narrowing and reduced testosterone levels (Phillips et al 1994). Men with low testosterone levels have been observed to have: premature atherosclerosis, increased visceral adipose tissue, hyperinsulinemia, and other risk factors for myocardial infarction (Phillips 2005). Insulin resistance has been shown to be associated with a decrease in Leydig cell secretion of testosterone (Pitteloud et al 2005). Muller and colleagues suggest that low endogenous total testosterone and SHBG levels increase the risk of metabolic syndrome in aging and aged men. They demonstrated that low levels of testosterone are related to lower insulin sensitivity and higher fasting insulin levels (Muller et al 2005). These authors speculate that testosterone might play a protective role in the development of metabolic syndrome, insulin resistance, diabetes mellitus and cardiovascular disease in aging men.

Dobs and colleagues found that men with an increased body mass index had both reduced testosterone and reduced high density lipoprotein (HDL) levels. Treatment with testosterone increased the levels of HDL (Dobs et al 2001). Rising levels of HDL are not a consistent finding with TRT. More often, however, one finds reduced total cholesterol, low density lipoprotein (LDL) cholesterol and triglyceride levels with TRT (Zgliczynski et al 1996; Whitsel et al 2001).

Smith and colleagues (2005) undertook a prospective study on the contribution of stress to coronary heart disease. Their study, which involved 2512 men aged 45 to 59 years, looked at a number of metabolic parameters. They found that an increased cortisol to testosterone ratio was associated with a high risk of coronary artery disease and that this risk was mediated by components of the insulin resistance syndrome. They reported that high cortisol and low testosterone levels are associated with a worsening of insulin resistance and that there is evidence to support the possibility of improving this pattern by treatment with testosterone.

Diabetes mellitus, obesity, metabolic syndrome

The definition of the metabolic syndrome continues to be a work in progress. Within the last decade a number of definitions have emerged each with its own set of criteria although there is considerable overlap among them. The most recent definition seems to enjoy considerable consensus. It requires central adiposity (>94 cm waist circumference) plus two of, increased triglycerides, decreased HDL cholesterol, hypertension, insulin resistance as evidenced by impaired glucose tolerance, or frank diabetes (Alberti 2005). Almost immediately on the heels of this consensus, came a number of specific chemical markers which have been proposed to complement the basic definition of the metabolic syndrome (Eckel et al 2005).

Adipose tissue contains high concentrations of aromatase thus accelerating the conversion of testosterone to estradiol (Wake et al 2007). Estradiol, in turn, suppresses gonadotropin secretion which reduces the output of testosterone (Chongthammakun and Terasawa 1993). Diabetes mellitus is associated with decreased levels of testosterone.

Individuals with metabolic syndrome are at increased risk for developing coronary artery disease and diabetes mellitus. Predicting who might develop the metabolic syndrome would allow preventive measures to be taken in addition to weight control and other lifestyle modifications such as cessation of smoking and increased exercise. It is known that with decreasing testosterone availability in aging males there is an increase in fat mass and decrease in lean body mass (van den Beld et al 2000), there are disorders of insulin and glucose metabolism (Haffner et al 1996) and dyslipidemia (Tsai et al 2004). Kupelian and colleagues (2006) in analyzing data from the Massachusetts Male Aging Study demonstrated that men with low levels of testosterone, sex hormone-binding globulin, or clinical androgen deficiency, especially men with a BMI of greater than 25, were at increased risk of developing the metabolic syndrome and hence, diabetes mellitus and/or coronary artery disease.

It is now well-established that elderly men with type 2 diabetes mellitus have reduced levels of testosterone (Barrett-Connor 1992; Betancourt-Albrecht and Cunningham 2003). It is known, however, that obese men and diabetic men have reduced levels of SHBG (Barrett-Connor 1990) which could account for the lower total testosterone levels found in diabetic men. Dhindsa et al (2004) studied 103 male patients who had type 2 diabetes mellitus using free testosterone (done by equilibrium dialysis) or calculated free testosterone which takes SHBG levels into account. Of the 103 patients, 57 had free testosterone by equilibrium dialysis and of these, 14 (25%) had a free T below 0.174 nmol/L and were considered hypogonadal. Using a total testosterone of 10.4 nmol/L (300ng/dl) as the lower limit of normal 45 patients (43%) were in the hypogonadal range. They also found that LH and FSH concentrations were significantly lower in the hypogonadal group. The authors thus concluded that hypogonadotropic hypogonadism was a common finding in type 2 diabetes irrespective of glycemic control, duration of disease or the presence of complications of diabetes or obesity.

The finding of hypogonadism in diabetic men is not just a scientific curiosity, it may have practical management implications. Kapoor and colleagues (2006) undertook a placebo-controlled double blind study to determine the effect of testosterone therapy on insulin resistance and glycemic control in hypogonadal men with type 2 diabetes. They found that men treated with testosterone had reductions in glycated hemoglobin insulin resistance, fasting blood sugar, waist circumference, waist/hip ratio and total cholesterol.

Autoimmune disease

There is an increased incidence of hypogonadism in men with rheumatoid arthritis. Tengstrand et al (2002) studied hormonal levels in 104 men with rheumatoid arthritis and 99 age-matched healthy men. They divided their subjects into 3 age groups: 30–49, 40–59, 60–69. Mean non-sex hormone binding globulin-bound testosterone (bioavailable testosterone) was lower in men with rheumatoid arthritis for each of the three groups. LH was also found to be lower in the patients with rheumatoid arthritis suggesting a hypothalamic-pituitary cause of the reduced bioavailable testosterone. Of the 104 men with rheumatoid arthritis, 33 had hypogonadism compared to 7 of the 99 healthy controls.

The converse is also true; there is an increased incidence of rheumatic/autoimmune disease in men with hypogonadism. Jimenez-Balderas et al (2001) carried out neuroendocrine, genetic and rheumatologic investigations in hypogonadal men. Of the 13 hypogonadal patients, 8 (61%) had rheumatic autoimmune disease (ankylosing spondylitis, systemic lupus erythemetosus, rheumatoid arthritis, dermatomyositis). There is a low frequency of those diseases (0.83%) in the general population.

Decreased testosterone production in men with rheumatoid arthritis is a common finding (Stafford et al 2000), and it is now generally recognized that androgens have the capacity to suppress both the hormonal and cellular immune response and so act as one of the body's natural anti-inflammatory agents (Cutolo et al 2002). This known anti-inflammatory action of testosterone has led to studying the effect of testosterone therapy in men with rheumatoid disease. Although not all studies have reported positive effects of testosterone treatment (Hall et al 1996), some studies do demonstrate an improvement in both clinical and chemical markers of the immune response (Cutolo et al 1991; Cutolo 2000). This observation would go along with more recent evidence that testosterone or its metabolites protects immunity by preserving the number of regulatory T cells and the activation of CD8+ T cells (Page et al 2006).

Narcotic dependence

Opioid substances are in common use both licit and illicit. Opiates are potent analgesics but they are also highly

addictive. They are frequently prescribed for both acute and chronic pain and when used chronically, often induce opiate dependence in the user. Pain clinics regularly use narcotic agents in many of their patients. Methadone, in particular, is regularly prescribed to opiate addicts who have entered a program aimed at reducing narcotic dosage and ultimately weaning the patient off it altogether. Most men who are on chronic high doses of an opiate become hypogonadal. This was first recognized in the 1970's when heroin addicts were found to have suppressed levels of testosterone (Brambilla et al 1977). Also suppressed were LH and FSH pointing to a probable inhibition of GnRH release.

Since then there have been many publications documenting suppressed testosterone and gonadotropins (Daniell 2006) in men using opioid medications whether these agents were administrated orally (Daniell 2002) or intrathecally (Finch et al 2000). Not only do opioids act centrally by suppressing GnRH, they also act directly on the testes inhibiting the release of testosterone by Leydig cells during stimulation with human chorionic gonadotropin (Purohit et al 1978). Although the large majority of men (and women) receiving opioids do develop hypogonadism, about 15 percent also develop central hypocorticism and 15 percent develop growth hormone deficiency (Abs et al 2000).

HIV/AIDS

Testosterone insufficiency has been associated with HIV infection in men (Dobs et al 1988). Early reports suggested that testosterone therapy may have an ameliorating effect on both depression and decreased energy in HIV infected men, even if testosterone levels were not reduced (Rabkin et al 1999; Grinspoon et al 2000; Rabkin et al 2000). Both depression and fatigue, however, are common features of HIV-positive men and may be associated with factors other than reduced levels of testosterone. The disease itself may induce depression and fatigue may be a consequence of the disease, per se, or of some of the medications used to control HIV.

Because of inconclusive or conflicting results of testosterone treatment studies reported in the literature, Rabkin and colleagues (2004) undertook a comparison study among testosterone, the anti-depressant, fluoxetine, and placebo in eugonadal HIV positive men. They found that neither fluoxetine nor testosterone were different from placebo in reducing depression, but that testosterone did have a statistically significant effect in reducing fatigue. It is note-worthy that fatigue was reduced with testosterone treatment even though virtually all the men in the study had testosterone levels within the reference range.

The message emanating from these accumulated studies is that HIV-infected men should have their testosterone levels measured and even if normal, a trial of testosterone treatment may be warranted in symptomatic men.

Hypogonadism in the aging male

As already indicated previously, testosterone levels, particularly bioavailable testosterone, fall with advancing age. This decline in testosterone availability may start to occur early in the forth decade but it usually becomes clinically manifest in the 50s and 60s. Although there is continuing debate about the best way to diagnose hypogonadism in the aging male, there appears to be a general consensus that symptomatic men with reduced levels of testosterone should be given a trial of testosterone therapy if there is no contraindication to do so (Bain et al 2007).

The reasons for considering such therapy become evident from the many associations, indicated above, that reduced testosterone has with a variety of both physiological functions (bone metabolism, muscle mass, cognitive function, libido, erectile function) and pathophysiological states (metabolic syndrome, diabetes mellitus, obesity, insulin resistance, autoimmune disease). Although a definitive long-term, large scale placebo-controlled double-blind study of testosterone therapy in the aging male has not yet been carried out, multiple shorter-term trials have suggested improvement by testosterone with a resultant enhancement of muscle mass, bone density, libido, erectile function, mood, motivation and general sense of well-being.

There are valid concerns about the safety of long-term treatment with testosterone particularly with respect to the cardiovascular system and the potential for stimulating prostate cancer development. There are no convincing hard data, however, to support these concerns. If anything, the data strongly suggest that adequate testosterone availability is cardioprotective and coronary risk factors such as diabetes, obesity and the metabolic syndrome are associated with reduced testosterone levels. It is certainly appropriate to avoid giving testosterone to men with prostate or breast cancer but it is not appropriate to accuse testosterone of inducing the development of de novo prostate cancers since evidence for this accusation is lacking (Wang et al 2004; Feneley and Carruthers 2006).

Conclusion

Testosterone is a hormone with multifaceted physiological functions and multiple associations with pathophysiological states. It is an important hormone in male reproductive and

metabolic function from intrauterine life to old age. In severe or classical hypogonadal states there is little controversy about the need to administer testosterone by an intramuscular, oral or transdermal formulation. There is controversy about making the diagnosis in the less severe cases of hypogonadism associated with the aging male but the current evidence suggests that this is efficacious in appropriately selected men and that there is little if any risk in giving aging symptomatic hypogonadal men a 6 month trial of therapy to determine whether symptoms will improve.

Testosterone is not a panacea for prolonging youth by warding off the aging process. It may, however, provide the appropriately selected symptomatic male with reduced testosterone availability assistance in helping that man move more gracefully into the senior years of his life.

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References

Abs R, Verhelst J, Maeyaert J, et al. 2000. Endocrine consequences of long-term intrathecal administration of opioids. *J Clin Endocrinol Metab*, 85:2215–22.

Adler RA. 2006. Epidemiology and pathophysiology of osteoporosis in men. *Curr Osteoporosis Rep*, 4:110–15.

Alberti KGMM. 2005. Conclusions from the 2004 IDF Consensus on the Metabolic Syndrome Presented at the 1st International Congress on "prediabetes" and the Metabolic Syndrome. Epidemiology, Management and Prevention of Diabetes and Cardiovascular Disease in Berlin, Germany, April 12, 2005.

Araujo AB, O'Donnell AB, Brambilla DJ, et al. 2004. Prevalence and incidence of androgen deficiency in middle-aged and older men: estimates from the Massachusetts Male Aging Study. *J Clin Endocrinol Metab*, 89:5920–6.

Azad N, Pitale S, Barnes WE, et al. 2003. Testosterone treatment enhances regional brain perfusion in hypogonadal men. *J Clin Endocrinol Metab*, 88:3064–8.

Bain J, Brock GE, Kuzmarov I for the International Consulting Group. 2007. Canadian Society for the Study of the Aging Male: Response to Health Canada's position paper on testosterone treatment. *J Sex Med*, 4:558.

Barrett-Connor E, Khan KT, Yen SS. 1990. Endogenous sex hormone levels in older adult men with diabetes mellitus. *Am J Epidemiol*, 132:895–901.

Barrett-Connor E. 1992. Lower endogenous androgen levels and dyslipidemia in men with non-insulin dependent diabetes mellitus. *Ann Intern Med*, 117:807–11.

Barrett-Connor E, Von Mühlen DG, Kritz-Silverstein D. 1999. Bioavailable testosterone and depressed mood in older men: The Rancho Bernardo study. *J Clin Endocrinol Metab*, 84:573–7.

Betancourt-Albrecht M, Cunningham GR. 2003. Hypogonadism and diabetes. *Int J Impot Res*, 15(Suppl 4):514–20.

Bhatia V, Chaudhuri A, Tomar R, et al. 2006. Low testosterone and high C-reactive protein concentrations predict low hematocrit in type 2 diabetes. *Diabetes Care*, 29:1–6.

Brambilla F, Sacchetti E, Brunetta M. 1977. Pituitary-gonadal function in heroin addicts. *Neuropsychobiology*, 3:160–6.

Carson CC, Lue TF. 2005. Phosphodiesterase type 5 inhibitors for erectile dysfunction. *BJU Int*, 96:257–80.

Chongthammakun S, Terasawa E. 1993. Negative feedback effects of estrogen on luteinizing hormone-releasing hormone release occur in pubertal, but not prepubertal ovarjectomized female rhesus monkeys. *Endocrinology*, 132:735–43.

Cutolo M, Balleari E, Giusti M, et al. 1991. Androgen replacement therapy in male patients with rheumatoid arthritis. *Arthritis Rheum*, 34:1–5.

Cutolo M. 2000. Sex hormone adjuvant therapy in rheumatoid arthritis. *Rheum Dis Clin North Am*, 26:881–95.

Cutolo M, Seriolo B, Villaggio B, et al. 2002. Androgens and estrogens modulate the immune and inflammatory responses in rheumatoid arthritis. *Ann NY Acad Sci*, 966:131–42.

Daniell HW. 2002. Hypogonadism in men consuming sustained-action oral opioids. *J Pain*, 3:377–84.

Daniell HW. 2006. Opioid-induced androgen deficiency. *Curr Opin Endocrinol Diabetes*, 13:262–6.

Davey RA, Morris HA. 2005. Effects of estradiol and dihydrotestosterone on ostsoblast gene expression in osteopenic ovariectomized rats. *J Bone Miner Metab*, 23:212–18.

Davis SR, McCloud P, Strauss BJ, et al. 1995. Testosterone enhances estradiol's effect on postmenopausal bone density and sexuality. *Maturitas*, 21:227–36.

Davis S, Walker K, Strauss B. 2000. Effects of estradiol with and without testosterone on body composition and relationships with lipids in postmenopausal women. *Menopause*, 7:395–401.

Dhindsa S, Prabhakar S, Sethi M, et al. 2004. Frequent occurrence of hypogonadatropic hypogonadism in type 2 diabetes. *J Clin Endocrinol Metab*, 89:5462–8.

Dobs AS, Dempsey M, Ladenson P. 1988. Endocrine disorders in men infected with human immunodeficiency virus. *Am J Med*, 84:611–16.

Dobs AS, Bachorik PS, Arver S, et al. 2001. Interrelationships among lipoprotein levels, sex hormones, anthropometric parameters, and age in hypogonadal men treated for 1 year with a permeation-enhanced testosterone transdermal system. *J Clin Endocrinol Metab*, 86:1026–33.

Dunajska K, Milewicz A, Szymczak J, et al. 2004. Evaluation of sex hormone levels and some metabolic factors in men with coronary atherosclerosis. *Aging Male*, 7:197–204.

Eckel RH, Grundy SM, Zimmet PZ. 2005. The metabolic syndrome. *Lancet*, 365:1415–28.

Emadi-Konjin P, Bain J, Bromberg IL. 2003. Evaluation of an algorithm for calculation of serum "Bioavailable" Testosterone (BAT). *Clinical Biochemistry*, 36:591–6.

Ergun-Longmire B, Auchus R, Papari-Zareei M, et al. 2006. Two novel mutations found in a patient with 17 alpha-hydroxylase enzyme deficiency. *J Clin Endocrinol Metab*, 91:4179–82.

Feldman HA, Longcope C, Derby CA, et al. 2002. Age trends in the level of serum testosterone and other hormones in middle-aged men: Longitudinal results from the Massachusetts Male Aging Study. *J Clin Endocrinol Metab*, 87:589–98.

Feneley Mr, Carruthers ME. 2006. Androgens, the prostate and safety of testosterone treatment. *Aging Male*, 9:4–Abs 9.

Finch PM, Roberts LJ, Price L, et al. 2000. Hypogonadism in patients treated with inrathecal morphine. *Clin J Pain*, 16:251–4.

Fink HA, Ewing SK, Ensrud KE, et al for the Osteoporotic Fractures in Men Study Group. 2006. Association of testosterone and estradiol deificiency with osteoporosis and rapid bone loss in older men. *J Clin Endocrinol Metab*, 91:3908–15.

Greenlee MW. 2000. Human cortical areas underlying the perception of optic flow:brain imaging studies. *Int Rev Neurobiol*, 44:269–92.

Grinspoon S, Corcoran C, Stanley T, et al. 2000. Effects of hypogonadism and testosterone administration on depression indices in HIV-infected men. *J Clin Endocrinol Metab*, 85:60–5.

Haffner SM, Shaten J, Stern MP, et al. 1996. Low levels of sex hormone-binding globulin and testosterone predict the development of non-insulin dependent diabetes mellitus in men. MRFIT Research Group. Multiple Risk Factors Intervention Trial. *Am J Epidemiol*, 143:889–97.

Hall RC, Hall RC. 2005. Abuse of supraphysiologic doses of anabolic steroids. *South Med J*, 98-550-5.

Hall GM, Larbre JP, Spector TD, et al. 1996. A randomized trial of testosterone therapy in males with rheumatoid arthritis. *Br J Rheumatol*, 35:568–73.

Harman SM, Metter EJ, Tobin JD, et al. 2001. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltmore Longitudinal Study of Aging. *J Clin Endocrinol Metab*, 86:724–31.

Hughes IA, Deeb A. 2006. Androgen resistance. *Best Pract Res Clin Endocrinol Metab*, 20:577–98.

Jimenez-Balderas FJ, Tapia-Serrano R, Fonseca ME, et al. 2001. High frequency of rheumatic/autoimmune diseases and untreated male hypogonadism with severe testicular dysfunction. *Arthritis Res*, 3:362–7.

Kalinchenko SY, Kozlov GI, Gontcharov NP, et al. 2003. Oral testosterone undecanoate reverses erectile dysfunction associated with diabetes mellitus in patients failing on sildenafil therapy alone. *Aging Male*, 6:94–9.

Kapoor D, Goodwin E, Channer KS, et al. 2006. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. *Eur J Endocrinol*, 154:899–906.

Katznelson L, Finkelstein JS, Schoenfeld DA, et al. 1996. Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism. *J Clin Endocrinol Metab*, 81:4358–65.

Kaufman JM, Vermeulen A. 2005. The decline of androgen levels in elderly men and its clinical and therapeutic implications. *Endo Rev*, 26:833–76.

Kopera H. 1993. Side-effects of anabolic steroids and contraindications. *Wien Med Wochenschr*, 143:399–400.

Kupelian V, Page ST, Araujo AB, et al. 2006. Low sex hormone-binding globulin, total testosterone, and symptomatic androgen deficiency are associated with development of the metabolic syndrome in non-obese men. *J Clin Endocrinol Metab*, 91:843–50.

Lamberts SW, van den Beld AW, van der Lely AJ. 1997. The endocrinology of aging. *Science*, 278:419–24.

MacLaughlin DT, Donahue PK. 2004. Review Article, Mechanisms of Disease. Sex determination and differentiation. *N Engl J Med*, 350:367–78.

McIntyre RS, Mancini D, Eisfeld BS, et al. 2006. Calculated bioavailable testosterone levels and depression in middle-aged men. *Psychoneuroendocrinology*, 31:1029–35.

Mills TM, Wiedmeier VT, Stopper VS. 1992. Androgen maintenance of erectile function in the rat penis. *Biol Reprod*, 46:342–8.

Moffat SD, Zonderman AB, Metter EJ, et al. 2002. Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. *J Clin Endocrinol Metab*, 87:5001–7.

Moffat SD, Zonderman AB, Metter EJ, et al. 2004. Free testosterone and risk for Alzheimer disease in older men. *Neurology*, 62:188–93.

Morelli A, Filippi S, Zhang XH, et al. 2005. Peripheral regulatory mechanisms in erection. *Int J Androl*, 28(Suppl 2):23–7.

Morley JE, Perry HM. 2003. Androgen treatment of male hypogonadism in older males. *J Steroid Biochem Mol Biol*, 85:367–73.

Muller M, Grobbee DE, den Tonkelaar I, et al. 2005. Endogenous sex hormones and metabolic syndrome in aging men. *J Clin Endocrinol Metab*, 90:2618–23.

Page ST, Amory JK, Bowman FD, et al. 2005. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. *J Clin Endocrinol Metab*, 90:1502–10.

Page ST, Plymate SR, Bremner WJ, et al. 2006. Effect of medical castration on CD4 + CD25+T cells, CD8+T cell IFN-gamma expression, and NK cells: a physiological role for testosterone and/or its metabolites. *Am J Physiol Endocrinol Metab*, 290:E856–63.

Paoletti AM, Congia S, Lello S, et al. 2004. Low androgenization index in elderly women and elderly men with Alzheimer's disease. *Neurology*, 62:301–3.

Phillips GB, Pinkernell Bh, Jing T-Y. 1994. The association of hypotestosteronemia with coronary artery disease in men. *Arterioscler Thromb*, 14:701–6.

Phillips G. 2005. Is atherosclerotic cardiovascular disease an endocrinological disorder? The estrogen-androgen paradox. *J Clin Endocrinol Metab*, 90:2706–11.

Pitteloud N, Hardin M, Dwyer A, et al. 2005. Increasing insulin resistance is associated with a decrease in Leydig cell testosterone secretion in men. *J Clin Endocrinol Metab*, 90:2636–41.

Pope HG, Cohane GH, Kanayama G, et al. 2003. Testosterone gel supplementation for men with refractory depression: a randomized, placebo-controlled trial. *Am J Psychiatry*, 160:105–11.

Purohit V, Singh HH, Ahluwalia BS, 1978. Failure of methadone-treated human testes to respond to the stimulatory effect of human chorionic gonadotrophin on testosterone biosynthesis in vitro. *J Endocr*, 78:299–300.

Rabkin JG, Wagner G, Rabkin R. 1999. Testosterone therapy for HIV+ men with and without hypogonadism. *J Clin Psychopharmacol*, 19:19–27.

Rabkin JG, Wagner GJ, Rabkin R. 2000. A double-blind placebo-controlled trial of testosterone therapy for HIV-positive men with hypogonadal symptoms. *Arch Gen Psychiatry*, 57:141–7.

Rabkin JG, Wagner GJ, McElhiney MC, et al. 2004. Testosterone versus fluoxetine for depression and fatigue in HIV/AIDS. A placebo-controlled trial. *J Clin Psychopharmacol*, 24:379–85.

Rosenthal BD, May NR, Metro MJ, et al. 2006. Adjunctive use of AndroGel (testosterone gel) with sildenafil to treat erectile dysfunction in men with acquired androgen deficiency syndrome after failure using sildenafil alone. *Urology*, 67:571–4.

Seeman E. 1997. Osteoporosis in men. *Baillieres Clin Rheumatol*, 11:613–29.

Seidman SN, Araujo AB, Roose SP, et al. 2002. Low testosterone levels in elderly men with dysthymic disorder. *Am J Psychiat*, 159:456–9.

Shahidi NT. 1973. Androgens and erythropoiesis. *N Engl J Med*, 289:72–80.

Sherwin BB, Gelfand M. 1987. The role of androgen in the maintenance of sexual functioning in oophorectomized women. *Psychosom Med*, 49:397–409.

Simon J, Braunstein G, Nachtigall L, et al. 2005. Testosterone patch increases sexual activity and desire in surgically menopause women with hypoactive sexual desire disorder. *J Clin Endocrinol Metab*, 90:5226–33.

Sinha-Hikim I, Cornford M, Gaytan H, et al. 2006. Effects of testosterone supplementation on skeletal muscle fibre hypertrophy and satellite cells in community – dwelling older men. *J Clin Endocrinol Metab*, 91:3024–33.

Smith MR, Finkelstein JS, McGovern FJ, et al. 2002. Changes in body composition during androgen deprivation therapy for prostate cancer. *J Clin Endocrinol Metab*, 87:599–603.

Smith GD, Ben-Shlomo Y, Beswick A, et al. 2005. Cortisol, testosterone and coronary heart disease. Prospective evidence from the Caerphilly Study. *Circulation*, 112:332–40.

Stafford L, Bleasel J, Giles A, et al. 2000. Androgen deficiency and bone mineral density in men with rheumatoid arthritis. *J Rheumatol*, 27:2786–90.

Szulc P, Claustrat B, Marchand F, et al. 2003. Increased risk of falls and increased bone resorption in elderly men with partial androgen deficiency: the MINOS study. *J Clin Endocrinol Metab*, 88:5240–7.

Tan RS, Pu SJ. 2003. A pilot study on the effects of testosterone in hypogonadal aging male patients with Alzheimer's disease. *Aging Male*, 6:13–17.

Tengstrand B, Carlstrom K, Hafstrom I. 2002. Bioavailable testosterone in men with rheumatoid arthritis – high frequency of hypogonadism. *Rheumatology (Oxford)*, 41:285–9.

Tivesten A, Moverare-Skrtic S, Chagin A, et al. 2004. Additive protective effects of estrogen and androgen treatment on trabecular bone in ovariectomized rats. *Bone Miner Res*, 19:1833–9.

Töhönen V, Ritzen EM, Nordqvist K, et al. 2003. Male sex determination and prenatal differentiation of the testis. In Söder O ed. The developing testis. physiology and pathophysiology. Karger, Basel. p 1–23.

Tremblay R. 2003. Measurement of testosterone. In Bain J ed. Mechanisms in andropause. Toronto: Mechanisms in Medicine Inc. p 42–8.

Tsai EC, Matsumoto AM, Fujimoto WY, et al. 2004. Association of bioavailable, free, and total testosterone with insulin resistance: influence of sex hormone-binding globulin and body fat. *Diabetes Care*, 27:861–8.

van den Beld AW, de Jong FH, Grobbee DE, et al 2000. Measures of bioavailable serum testosterone and estradiol and their relationship with muscle strength, bone density, and body composition in elderly men. *J Clin Endocrinol Metab*, 85:3276–82.

Vermeulen A, Verdonck L, Kaufman JM. 1999. A critical evaluation of simple methods for the estimation of free testosterone in serum. *J Clin Endocrinol Metab*, 84:3666–72.

Wake DJ, Strand M, Rask E, et al. 2007. Intra-adipose sex steroid metabolism and body fat distribrution in idiopathic human obesity. *Clin Endocrinol (Oxf)*, 66:440–6.

Wang C, Alexander G, Berman N, et al. 1996. Testosterone replacement therapy improves mood in hypogonadal men: a clinical research center study. *J Clin Endocrinol Metab*, 81:3578–83.

Wang C, Swerdloff RS, Iranmanesh A, et al. The Gel Study Group. 2000. Transdermal testosterone gell improves sexual function, mood, muscle strength and body composition parameters in hypogonadal men. *J Clin Endocrinol Metab*, 85:2839–53.

Wang C, Cunningham G, Dobs A, et al. 2004. Long-term testosterone gel (Androgel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass and bone mineral density in hypogonadal men. *J Clin Endocrinol Metab*, 89:2085–98.

Webb CM, McNeill JG, Hayward CS, et al. 1999. Effects of testosterone on coronary vasomotor regulation in men with coronary heart disease. *Circulation*, 100:1690–6.

Whitsel EA, Boyko EJ, Matasumoto AM, et al. 2001. Intramuscular testosterone esters and plasma lipids in hypogonadal men: a meta-analysis. *Am J Med*, 111:261–9.

Zgliczynski S, Ossowski M, Slowinska-Srzednicka J, et al. 1996. Effect of testosterone replacement therapy on lipids and lipoproteins in hypogonadal and elderly men. *Atherosclerosis*, 121:35–43.